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10/591,587	10/23/2006	Shinichi Hirose	2006_1477A	3395

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WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,587	HIROSE ET AL.	
	Examiner	Art Unit	
	KELAGINAMANE T. HIRIYANNA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/04/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to Application fled on 09/05/2006.

Claims 1-4 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic rat whose genome comprises a mutant transgene CHRNA4 comprisng a mutation that corresponds to S284L mutation in human CHRNA4 of SEQ ID NO:1 and is operably linked to a promoter and expressed in brain of the transgenic rat that is established by a normal developmental route (normal ontogenesis) and wherein said transgenic rat develops a spontaneous epileptic seizure during sleep and thus useful as a epilepsy model, is not enabled for an epilepsy model using any non-human animal that comprises said transgene, does not enable any non-human animal comprising an inoperable transgene that does not express in brain, does not enable any said transgenic rat/animal wherein the normal complement of chrna4 is over expressed, does not enable establishing said transgenic rat/animal by any ontogenesis of a totipotent cell, does not enable any progeny of said transgenic rat/animal. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At issue, under the enablement requirement of 35 U.S.C. 112, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. “Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based of the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of the ordinary skill in the art have to go through ‘’undue experimentation” in order to practice the invention.

Nature of the invention: The invention relates to establishing a transgenic animal that models specific epilepsy in humans known as ADNFLE and that is due to Ser284Leu mutation in CHRNA4 subunit of acetylcholine receptor in humans. The nature of the invention was such that said skilled in the artisan would not have been able to make or use the invention for its fully claimed scope without undue experimentation.

Breadth of the claims And Guidance Provided in the Specification: The scope of the invention encompasses any using any non-human animal that comprises a any non-human animal CHRNA4 mutant transgene containing a mutation that corresponds to S284L mutation of human CHRNA4 irrespective of whether it is operable or not, whether it is expressed in brain or not, irrespective of the levels of expression of the endogenous normal complements of the transgene, and establishing said transgenic animal by any route of ontogenesis. The claims in their breadth further encompass any progeny of said transgenic animal as an epilepsy model irrespective of the way it is bread.

The specification teaches only teaches regarding developing transgenic rat wherein the transgene is a rat mutant ortholog (SEQ ID NO:2) of human CHRNA4 gene where in the mutation in said rat transgene (S286L) corresponds to a mutant human CHRNA4 (S284L), that causes a phenotype of ADNFLE. The specification teaches such transgene when expressed in brain of a rat with a normally expressed background of the endogenous wild type complement of the transgene, induces an ADNFLE-type phenotype in the rat (for example see paragraphs 0019-0021 of the specification).

The specification does not teach any other enabled examples of any other non-human transgenic animal or non-human animal model of epilepsy expressing said mutation. Thus in the absence of representative number of enabled examples in the specification commensurate with the breadth of the claims one of ordinary skill in the art would conclude that the invention is unpredictable and would require undue experimentation to practice the invention in its full scope. Applicants' should note that the

test is whether the number of claimed genus/or species of transgenic animals that model the specific epilepsy as instantly claimed provided an adequate basis for inferring that the invention has generic applicability.

***State of the Art, the Predictability of the Art*:** At about the effective filing date of the present application art is unpredictable with regard to transgenic animals with the transgene comprising a mutation expressing the desired phenotypes and the stability predictability of such transgenes over generations. Art is still unpredictable regarding the use of. Further the mere capability to perform gene transfer in a rat or mouse is not enabling for all non-human animals because a desired phenotype cannot be predictably achieved by simply introducing transgene constructs (reviewed in Bishop Reproductive Nutrition and Development 36: 607-616, 1996; Rulicke and Hubischer, Experimental Physiology 85: 589-601, 2000) of the types recited in the claims. Transgene that is not expressed is as good as having it in or still worse and as such it provides no information at all about the function of the transgene except probably for the side-effects of having a foreign nucleic acid in the genome. Unpredictability of the phenotypes in conventional transgene introduction, as is in the instant application, arises due to transgene random integration into the host genome and subsequent aberrations namely poor expression, temporally and/or spatially aberrant expression, position effects etc. Further unpredictability arises owing to the functional and physiological effects of the expressed transgene (foreign gene), interference of the redundant native genes, induction of compensatory processes, gene silencing effects as well as due to the influence of genetic background and the phenomenon of imprinting (reviewed in Rulicke and

Hubischer, Experimental Physiology 85: 589-601, 2000; entire article; p.595 1st col. 1st paragraph). Further it is currently unpredictable that a human disease causing mutation when introduced into any animal by knock-in or in the form of a mutant transgene would predictably generate the disease phenotype of the corresponding to in a human carrier of the mutation. Only to a limited extent the rodents (mouse especially) have been reasonably successful as disease models. However, it is highly upredictable with regard to use of any animal for this purpose. For example it is not clear what a molluscan (snail) or a nematode or other lower invertebrate and other vertebrate animals may exhibit a phenotype corresponding to ADNFLE when introduced with a transgene of the instant invention. The Applicant here further claims that any progeny of the said transgenic animal would be able to or retain the transgene and the phenotype. However, it is well known in the art that such is not true. If a transgenic non-human animal (example a mouse or rat) one copy of the incorporated transgene as well as the phenotype is bread to a wild type strain containing the transgene (even assuming residing on an autosome) the transgene and the phenotype could be lost or not inherited in nearly one fourth of the second generation of the offsprings (progeny). Thus any progeny of the transgenic animal could not possibly serve as the disease models. Thus the unpredictability in the art, at the time of instant filing, regarding phenotype of transgenic animals is such that one of ordinary skill in the art finds the claimed invention highly unpredictable and cause undue experimentation to practice the invention in its full claimed scope.

Amount of experimentation necessary: Because of the lack of sufficient and representative working examples of broadly claimed transgenic animals, insufficient guidance and direction provided by Applicant, the inherent unpredictability of the art, and the nature of the invention, one of skill in the art would be required to perform a large amount of experimentation to make and/or use the invention in its full scope as claimed by Applicant. Such experimentation would be required generate large number of animals with representative samples by different phyla of animals, identifying corresponding gene and generating the corresponding mutation to human CHRNA4.S284L mutation Further these claims are not enabled because one of skilled in the art, at the date of filing, would not be able to rely upon the state of the art in order to successfully predict a priori the what the corresponding phenotypes would for those animals and would they be able to serve as the disease model for ADNFLE . Accordingly, in view of the lack of teachings and unpredictability in the art and lack of enabled guidance provided by the specification with regard to an enabled use of the invention as claimed as of around the filing date of instant application and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4 are rejected under 102(a) as being anticipated by Saito et al., (2004, J. Pharmacol. Sci. 93 (Suppl. I):102P; art of record).

The above claims are drawn to a non-human transgenic animal model for epilepsy that comprises a non-human animal CHRNA mutant transgene that carries a mutation corresponding to human-CHRNA-S284L of SEQ ID NO:1 and said transgenic animal has a phenotype of developing spontaneous epileptic seizures during sleep. In further limitations said transgene is fused to a promoter of a gene that is specifically expressed in cerebrum cortex and hippocampus. In still further limitations said transgenic animal is a rat having the nucleotide SEQ ID NO:2 which carries nucleotide base changes at position 865 from C to T and at position 866 from T to C.

Regarding claims 1-2 Saito teaches a transgenic rat animal model for epilepsy that comprises a CHRNA mutant transgene that carries a mutation corresponding to human CHRNA S284L (Abstract). SEQ ID NO:1 is known in the prior art and is the human sequence and further the association of epilepsy with S284L was also well established in the prior art. Sato reference thus clearly teaches the same invention as the instant one. Regarding claims 3 and 4 the position of nucleotide changes indicated for rat nucleotide sequence of SEQ ID NO:2 (corresponding to rat amino acid S286) corresponds to human CHRNA S284 taught in the prior art.. Further, in rat genome, the transgene which incorporates into a chromosome (encompassing any rat chromosome) certainly would

have a very high chance of being linked (or fused) with gene/s and/or gene promoter/s, that are inherently present on the chromosome and specifically express in cerebrum and/or hippocampus of rat brain. Thus the cited art clearly anticipates the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 are rejected under 35 USC 103 (a) as being unpatentable over Rozycka et al (2003, Epilepsia 44:1113-1117; art of record) in view Matsuhima et al (2002, Epilepsy Research 48:181-186; art of record).

The above claims are drawn to a non-human transgenic animal model for epilepsy that comprises a non-human animal CHRNA mutant transgene that carries a mutation corresponding to human-CHRNA-S284L of SEQ ID NO:1 and said transgenic animal has a phenotype of developing spontaneous epileptic seizures during sleep. In further limitations said transgene is fused to a promoter of a gene that is specifically expressed in cerebrum cortex and hippocampus. In still further limitations said transgenic animal is a rat having the nucleotide SEQ ID NO:2 which carries nucleotide base changes at position 865 from C to T and at position 866 from T to C.

Regarding claims 1-4 Rozycka teaches that a missense mutation S284L in human CHRNA4, a subunit of acetylcholine receptors in brain, causes an autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) in humans (entire article, abstract, p.1113 col.2, 2nd paragraph). Rozycka however does not teach that a corresponding mutation when introduced into a non-human animal ortholog of CHRNA4 or transfered as a transgene would cause epilepsy in the non h-human animal.

Regarding above claims Matsuhima clearly teaches that the electrophysiological characteristics of a acetylcholine receptor with a rat chrna4 mutant with a mutation corresponding to Ser284Leu of CHRNA4 and reconstituted in xenopus oocytes produced receptor with changed electrophysiological properties (entire article, abstract). This suggested that a mutation in amino acid corresponding Ser284 of CHRNA4 in non-human animal systems lead to reduced acetylcholine receptor activity similar to that is found in alpha4-subunit mutation harboring of ADFNLE patients (entire article; abstract; p.182 col.1-2; p.184 col.2 bridging p.185). Matsuhima also teaches that the corresponding location (position#) of the amino acid to S284 of CHRNA4 may vary different animals (p.182 col.1, 3rd paragraph).

Regarding claims 3 and 4 the position of nucleotide changes indicated for rat nucleotide sequence of SEQ ID NO:2 (rat amino acid S286) corresponds to human CHRNA S284 as taught in the prior art. The prior art clearly teaches several sequence alignment methodologies (e.g. Clustal-W sequence alignment program) that one of skill could use to figure out the corresponding positions in the orthologs and in other phylogenetically related genes. Further, in rat genome, the transgene which incorporates

into a chromosome (encompassing any rat chromosome) certainly would have a very high chance of being linked (or fused) with gene/s and/or gene promoter/s, that are inherently present on the chromosome and specifically express in cerebrum and/or hippocampus of rat brain.

Thus it would have been obvious for one of ordinary skill in the art to generate a transgenic animal by introducing a corresponding mutation that causes epilepsy (ADFNLE) in humans as taught by Rozycka and Matsuhima into a corresponding CHRNA subunit amino acid sequence as taught by Matsuhima. One of ordinary skill in the art would have been motivated to make and use a transgenic non-human animal with a corresponding human disease causing mutation, as it would provide an appropriate model system for drug screening and experimental therapeutic purposes. One of skill in the art would have reasonable expectation of success making using a transgenic mutant animal with a mutation corresponding to S284L of humans because the prior art clearly teaches that the phenotype associated CHRNA4 S284L human mutation could be transferred in to a non-human animal systems by creating mutant acetylcholine receptors with reduced activity and art further amply teaches the general methodologies for generating mutant genes and for generating transgenic animals.. Thus, the claimed invention was *prima facie* obvious.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.,* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.,* may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

/Robert M Kelly/

Primary Examiner, Art Unit 1633